Proton MRSI of the Limbic System in Autism at 3.0 Tesla

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Introduction Autism is a severe developmental disorder characterized by impairments in social interactions, communication, and restricted and repetitive behaviour. Abnormalities of the limbic system (comprising the hippocampus, parahippocampal gyrus, amygdala, cingulate gyrus, septal nuclei, anterior thalamus), which is associated with memory, learning and emotion, may underlie some of the core clinical symptoms of autism. Evidence for such abnormalities exists from post-mortem studies of patients with autism, which have revealed densely packed neural tissue in the limbic system, specifically in the hippocampus and anterior cingulate (1, 2). Functional and structural neuroimaging studies of autism have also found abnormalities associated with this system (3, 4). In the present study, children and adolescents with autism and a control group of healthy children were imaged using ^{1}H-MRSI to evaluate levels of ^{1}H brain metabolites in specific components of the limbic system. We hypothesize that subjects with autism will exhibit abnormal metabolite levels or asymmetries in limbic system structures.

Methods Twenty-three males with autism (mean age 10.2 (3.3), range 6-17 years, non-verbal IQ>70) and 25 healthy control males (mean age 10.8 (2.4), range 6-16 years, IQ>70) were recruited from the local community. The groups did not differ in age, sex, race, or non-verbal IQ, although significantly more patients were left-handed. A non-verbal intelligence of less than 70 and history of seizures were exclusionary. Six patients were medication-free at the time of scanning, 7 were medication naïve, while the remainder were being treated with stimulants, antipsychotics, and/or antidepressants. Experiments were performed late at night while subjects were asleep, and 17 patients were imaged under sedation using oral midazolam. Parental informed written consent, approved by the local Research Ethics Board, was provided prior to scanning.

A 3.0-T head-only research scanner (IMRIS, Winnipeg, Canada) with a quadrature head coil was used for all imaging experiments in this study. Standard T_1-weighted localizer images and axial multi-echo images for radiological assessment were initially acquired. This was followed by a 3-D MP-RAGE acquisition (1.2-mm isotropic voxels, TI/TE/TR=200/5/11 ms, flip angle 12 degrees, inter-segment repeat time 3.3 s), to be used for segmented regional volumetric analysis and MRSI partial volume correction. Localized proton spectra were acquired with an interleaved, multi-slice spin-echo MRSI sequence using slice-selective adiabatic inversion for extra-cranial lipid nulling (TI/TE/TR=230/135/1800 ms, FOV=280 mm, 35x35 circularly-bounded k-space acquisition, 30 minute scan time) (5). Two 10-mm thick oblique-axial slices (Figure 1a,b) were excited with numerically optimized RF pulses, yielding nominal voxel size of 8x8x10 mm (~1.0 cc effective voxel size after k-space filtering). Water suppression was performed during the inversion time, using the adiabatic WASHCODE technique (6), which provided good insensitivity to RF inhomogeniety, and eliminated the time-consuming task of optimizing the water-suppression pulses for each subject. T_1-weighted images were acquired at the same slice positions as the MRSI acquisition for anatomical correlation, and B_1-maps (7) were acquired to correct MRSI signal levels for RF field inhomogeneity. The full examination took approximately 1 hour.

MRSI datasets were first processed using k-space extrapolation to reduce ringing artifact from residual extra-cranial lipid signal (8). Using the T_1-weighted anatomical correlation images, voxels were selected for spectral analysis from left and right anterior cingulate, posterior hippocampus, and anterior-medial thalamus (Figure 1c). After subtraction of the residual water signal, fit using HLSVD, unfiltered spectra were fit in the time domain using prior knowledge from *in vitro* metabolite solutions using a constrained Marquardt-Levenberg minimization algorithm (9). The fitted metabolite signal amplitudes were corrected for coil load (10) and B_1 inhomogeneity. A 2x2x3 mixed ANOVA (diagnosis x hemisphere x region) was used to assess differences in regional metabolite levels separately for NAA, total creatine (Cre) and choline-containing compounds (Cho).

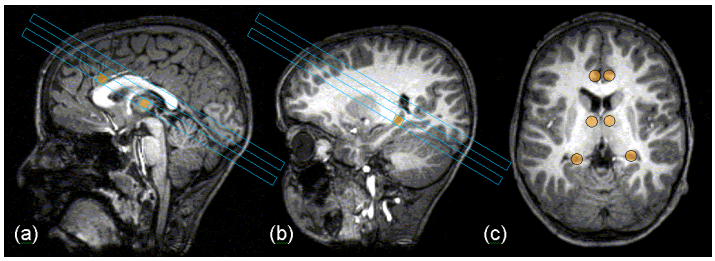

Figure 1: MP-RAGE images showing MRSI slice positions intersecting with (a) anterior cingulate and thalamus, (b) posterior hippocampus. Voxels were selected from the lower slice, as shown in (c).

Results A significant 3-way interaction was observed both for NAA and Cre ($p < 0.05$; see Figure 2). Choline levels did not differ significantly between groups. In protected post-hoc *t*-tests, NAA levels were found to be significantly higher in the right anterior cingulate of patients relative to controls (~8%, $p = 0.04$), and showed a tendency toward lower levels in right posterior hippocampus (~9%, $p = 0.10$). Creatine levels were significantly reduced in right anterior cingulate of patients relative to controls (~15%, $p = 0.04$).

Discussion These results provide further evidence for abnormalities of the limbic system in patients with autism. Given the putative role of NAA as a marker for functional neurons, these findings may indicate changes in the density or metabolic activity of neural tissue in components of the limbic system. Potential confounding effects of metabolite T2 decay, patient medication and sedation limit this study.

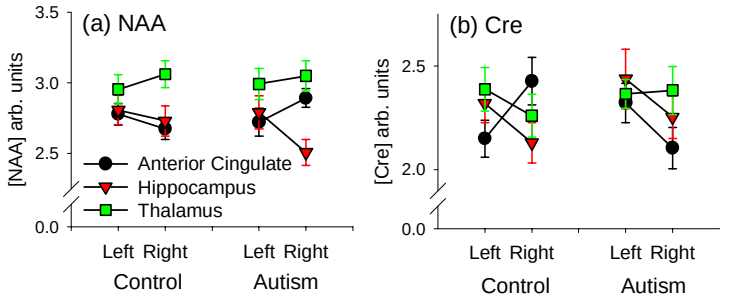

Figure 2: Mean metabolite concentration (±SE) in arbitrary units. (a) NAA and (b) Creatine for patients and controls in left and right limbic structures. Significant *region* x *hemisphere* x *diagnosis* interaction was observed ($p < 0.05$) for NAA and Creatine.

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